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C2C CAA CAB CKH CLA CLH C1472 C1604 C1626 C1745 C213 C215 C22Y C220 C247 C25Y C250 C252 C253 C28X C280 C282 C29X C29Y C30Y C305 C32Y C320 C321 C322 C323 C326 C34Y C342 C35X C351 C355 C36Y C364 C604 C62X C620 C625 C630 C634 C670 C672 C675 C713 C723 C746 C747 C80Y C802
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GB 2013679 A GB 1519557 A GB 1517403 A
NL 7902400 A NL 7804136 A

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UK CL (Edition J) C2C CKH CLA CLM
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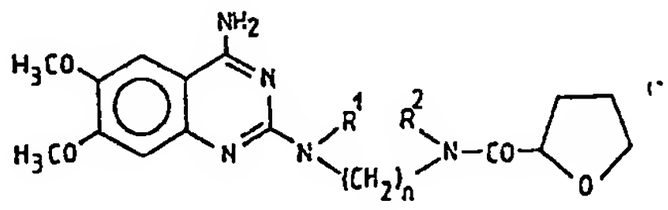
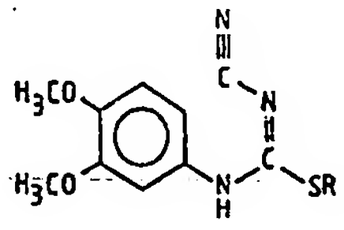
(54) Process for the preparation of quinazoline derivatives

(57) The invention relates to the preparation of quinazoline derivatives

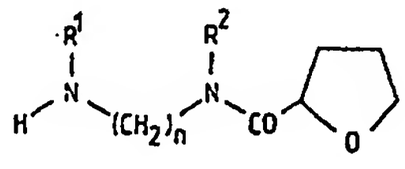


[wherein
R^1 and R^2 may be the same or different and stand for hydrogen or lower alkyl or together form an ethylene or trimethylene group, and
n is the integer 2 or 3
and pharmaceutically acceptable acid addition salts thereof, which comprises
a) reacting an isothiourea derivative



(III)

[wherein R stands for alkyl or aralkyl with an amine



(IV)

This print incorporates corrections made under Section 117(1) of the Patents Act 1977.

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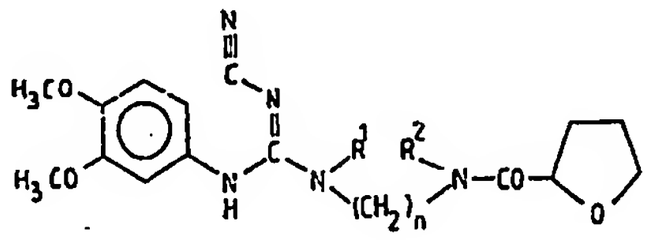
(wherein R^1, R^2 and n are as stated above).

At temperatures below 130°C, the reaction proceeds via an intermediate



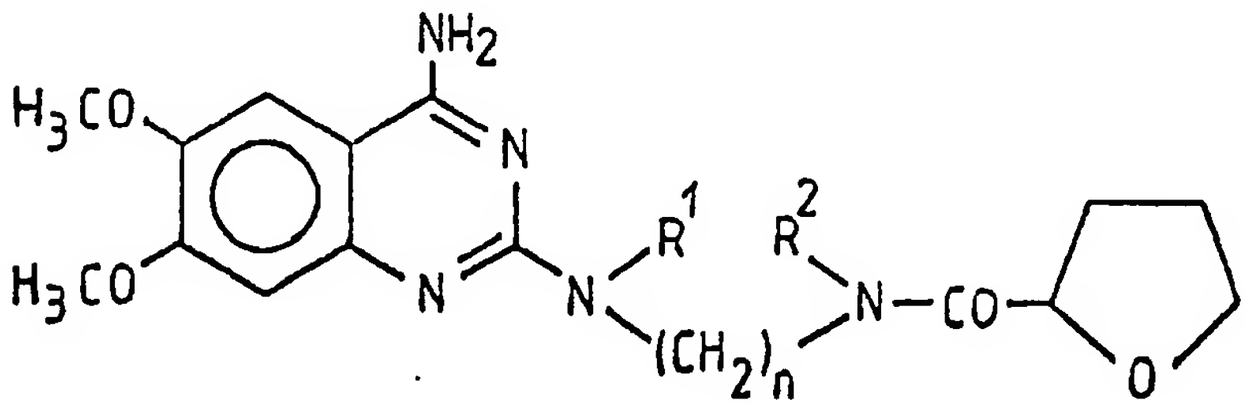
(II)

(wherein R^1, R^2 and n are as stated above); which is claimed *per se*.

PROCESS FOR THE PREPARATION OF QUINAZOLINE DERIVATIVES

This invention relates to a new process for the preparation of quinazoline derivatives, new intermediates useful in the said process and also to a process for the preparation of the said new intermediates.

According to an aspect of the present invention there is provided a process for the preparation of quinazoline derivatives of the general Formula I



(I)

/wherein

R^1 and R^2 may be the same or different and stand for hydrogen or lower alkyl or together form an ethylene ($-CH_2-CH_2-$) or trimethylene ($-CH_2-CH_2-CH_2-$) group; and

n is the integer number 2 or 3/

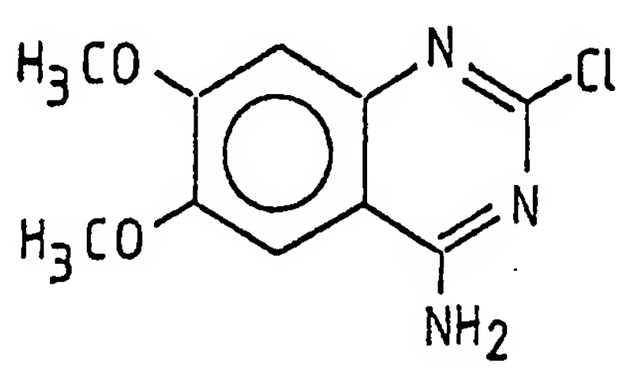
and pharmaceutically acceptable acid addition salts thereof.

The general Formula I comprises all isomers and tautomers and the present invention encompasses a process for the pre-

paration of all isomers and tautomers of the compounds of the general Formula I.

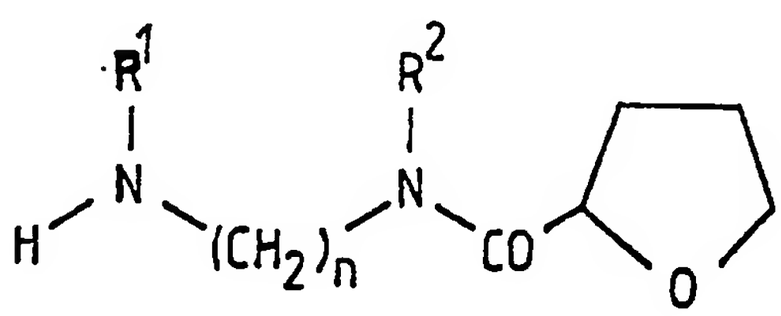
The compounds of the general Formula I are known pharmaceutical active ingredients useful as antihypertensive agents due to their α_1-receptor blocking activity.

The compounds of the general Formula I may be prepared either by reacting 4-amino-6,7-dimethoxy-2-chloro-quinazoline of the Formula IX



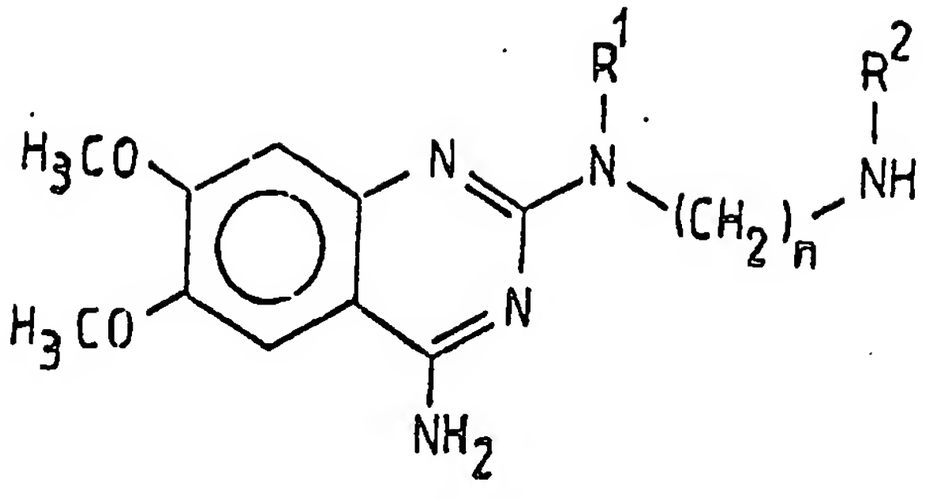
(IX)

with an amine of the general Formula IV



(IV)

(wherein R^1, R^2 and n are as stated above) or by reacting the compound of the Formula IX with the corresponding diamine to yield a compound of the general Formula V



(V)

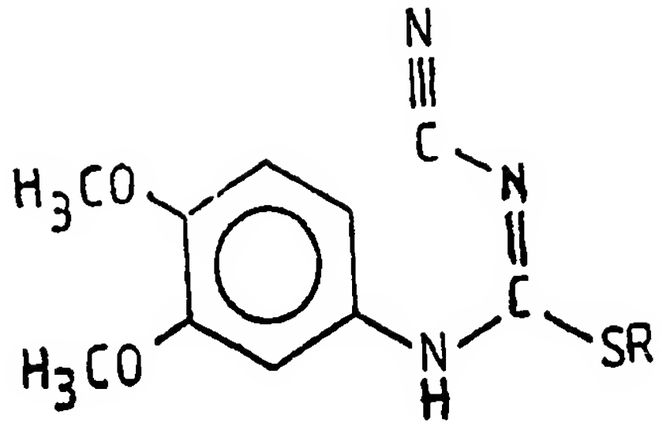
(wherein R^1, R^2 and n are as stated above) and subjecting the compound thus obtained to acylation (West-German patent No. 2,646,186; Belgian patents Nos. 879,730 and 873,909 and French patent No. 2,468,595).

The disadvantage of the above methods is that the starting material of the Formula IX is rather difficultly available and can be prepared from veratrum aldehyde by means of a seven-step synthesis and some of the steps of the said synthesis can be accomplished only with very low yields /J. Med. Chem. 20, 146 (1977)/.

It is the object of the present invention to provide a process for the preparation of the compounds of the general Formula I, which eliminates the above drawbacks of the known procedures.

According to an aspect of the present invention there is provided a process for the preparation of compounds of the general Formula I (wherein R^1, R^2 and n are as stated above) and pharmaceutically acceptable acid addition salts thereof which comprises

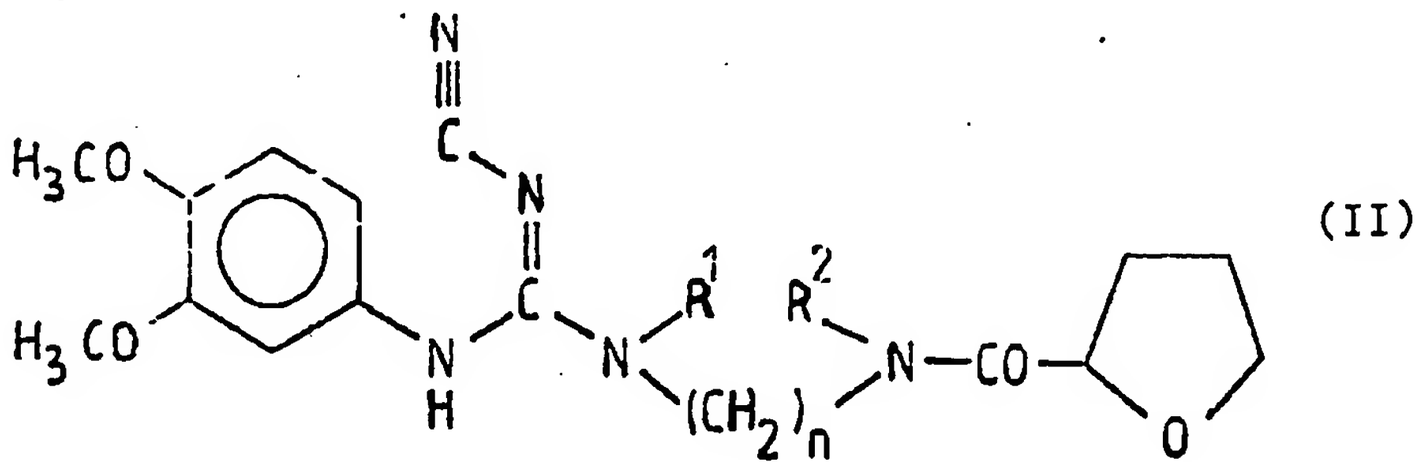
a) reacting an isothiourea derivative of the general Formula III



(III)

/ wherein R stands for lower alkyl or phenyl-lower alkyl, where the phenyl ring of the latter group may be optionally substituted by one or more lower alkyl group(s) and/or halogen atom(s)/ with an amine of the general Formula IV (wherein R^1, R^2 and n are as stated above) at a temperature between 150 °C and 280 °C; or

b) cyclising a compound of the general Formula II



(II)

(wherein R^1, R^2 and n are as stated above) optionally in the presence of a catalyst;

and, if desired, converting a compound of the general Formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

The present invention is based on the surprising recogni-

tion that the compounds of the general Formula I can be readily prepared by thermal or catalytic cyclisation of the new compounds of the general Formula II, never disclosed in prior art.

The term "lower alkyl" used throughout the specification relates to straight or branched chain saturated hydrocarbon groups comprising 1-4 carbon atoms (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, tert.-butyl etc.). The term "phenyl-lower alkyl" relates to lower alkyl groups as defined above substituted by a phenyl group (e.g. methyl, β-phenyl-ethyl etc.). The term "halogen" encompasses the fluorine, chlorine, bromine and iodine atoms and is preferably fluorine, chlorine or bromine.

The new starting materials of the general Formula II can be prepared by reacting an isothiourea derivative of the general Formula III and an amine of the general Formula IV and can be either isolated or directly cyclised into the desired quinazoline derivative of the general Formula I *in situ* without isolation.

The starting materials of the general Formula III are known compounds [J. Heterocycl. Chem. 23, 401 (1986)] or can be prepared in an analogous manner to the process disclosed in Hungarain patent No. 181,743.

The starting materials of the general Formula IV are known amines disclosed in prior art (DOS No. 2,646,186; Belgian patents Nos. 873,909 and 879,730 and French patent No. 2,468,595).

According to process a) an isothiourea derivative of the

general Formula III is reacted with an acylated amine of the general Formula IV in an inert organic solvent which has a boiling point above 150 °C. It is preferred to use dimethyl formamide, dimethyl acetamide, N-methyl-pyrrolidone, hexamethylphosphoric triamide, dimethyl sulfoxide, sulfolane, dimethylene glycol dimethyl ether, diethylene glycol diethyl ether, diphenyl ether, nitrobenzene, dichlorobenzene or tetrahydronaphthalene as solvent. According to a particularly preferred form of realization of process a) the reaction of the compounds of the general Formula III and IV is carried out in dimethylene glycol dimethyl ether or dimethyl formamide at a temperature between 150 °C and 220 °C, particularly preferably at 160-180 °C. It is preferred to use as starting material a compound of the general Formula III wherein R stands for methyl.

According to process b) a compound of the general Formula II is converted into the desired quinazoline derivative of the general Formula I by ring-closure. The cyclization reaction is accomplished either by heating (thermal cyclization) or in the presence of a suitable catalyst.

Thermal cyclization of the compounds of the general Formula II may be carried out in the absence or presence of a solvent. As reaction medium an inert solvent having a boiling point of 150-280 °C - preferably boiling between 150 °C and 220 °C - may be used. It is thus preferred to use as reaction medium a solvent which has a boiling point above 150 °C, particularly dimethyl formamide, dimethyl acet-

amide, N-methyl-pyrrolidone, hexamethyl-phosphoric triamide, dimethyl sulfoxide, sulfolane, dimethylene glycol dimethyl ether, diethylene glycol diethyl ether, diphenyl ether, nitrobenzene, dichlorobenzene, tetrahydronaphthalene etc. It is particularly preferable to work in dimethylene glycol dimethyl ether or dimethyl formamide as reaction medium.

Cyclisation of the compounds of the general Formula II may also be accomplished in a solvent in the presence of a catalyst at a temperature between 25 °C and 130 °C, preferably at 70-100 °C. Phosphorous oxychloride may preferably act as solvent while as catalyst preferably phosphorous trichloride, phosphorous pentachloride, phosphorous tribromide or a Lewis acid may be used. As Lewis acid preferably aluminium chloride, boron trifluoride, boron trifluoride etherate, zinc chloride, stannous chloride etc. may be applied. One may particularly advantageously work in phosphorous oxychloride as solvent, in the presence of phosphorous trichloride as catalyst.

The compounds of the general Formula I can be isolated from the reaction mixture by methods known per se.

The compounds of the general Formula I can be converted into the pharmaceutically acceptable acid addition salts by methods known per se. Thus the compound of the general Formula I can be reacted in a solvent with the corresponding inorganic or organic acid (e.g. hydrogen chloride, hydrogen bromide, sulfuric acid, maleic acid, fumaric acid etc.).

According to a particularly preferred form of realiza-

tion of the present invention a compound of the general Formula I is prepared, wherein R^1 stands for methyl, R^2 is hydrogen and n = 3, by use of the corresponding starting materials of the general Formulae II, III and IV, wherein R^1, R^2 and n are as stated above.

According to an other particularly preferred form of realization of the process of the present invention a compound of the general Formula I is prepared wherein R^1 and R^2 form together an ethylene group ($-CH_2-CH_2-$) and n = 2, by use of the corresponding starting materials of the general Formulae II, III and IV, wherein R^1, R^2 and n are as stated above.

According to a further aspect of the present invention there are provided new N-cyano-carboxamidine derivatives of the general Formula II (wherein R^1, R^2 and n are as stated above).

According to a still further aspect of the present invention there is provided a process for the preparation of the new intermediates of the general Formula II which comprises reacting an isothiourea derivative of the general Formula III /wherein R stands for lower alkyl or phenyl-lower alkyl whereby the phenyl ring of the latter group may be optionally substituted by one or more lower alkyl group(s) and/or halogen atom(s)/ with an amine of the general Formula IV (wherein R^1, R^2 and n are as stated above) at a temperature not exceeding 130 ^oC.

The reaction is carried out in an inert solvent, preferably an alcohol or a polar aprotic solvent. It is

particularly preferred to accomplish the reaction in isopropanol or dimethyl formamide as solvent. The reaction is carried out at a temperature not exceeding 130 °C, preferably at a temperature between 25 °C and 130 °C.

The compounds of the general Formula II can be isolated from the reaction mixture by methods known per se, advantageously by evaporating the solvent and subjecting the residue to crystallization.

The advantage of the present invention is that the desired compounds of the general Formula I can be prepared from readily available starting materials by a simple easily feasible economical method and in highly pure form.

Further details of the present invention are to be found in the following Examples without limiting the scope of protection to the said Examples.

Example 1

4-(2-Tetrahydro-furoyl)-piperazine-1-/N-cyano-N'-(3,4-dimethoxyphenyl)7-carboxamidine

A solution of 25.1 g (0.1 mole) of N-cyano-N'-(3,4-dimethoxyphenyl)-S-methyl-isothiourea and 27.6 g (0.15 mole) of N-(tetrahydro-2-furoyl)-piperazine in 150 ml of isopropanol is heated to boiling for 2 hours. The reaction mixture is cooled, the isopropanol is removed and the residual crude product (38.2 g) is recrystallized from ethanol. Thus 35.7 g of the desired compound are obtained, yield 92%, mp.: 182-184 °C.

Example 2

4-(2-Tetrahydro-furoyl)-homopiperazine-1-/¯N-cyano-N'--N'-(3,4-dimethoxyphenyl)7-carboxamidine

One proceeds as described in Example 1 except that N-(tetrahydro-2-furoyl)-piperazine is replaced by 19.8 g (0.1 mole) of N-(tetrahydro-2-furoyl)-homopiperazine and as solvent instead of the isopropanol 50 ml of dimethyl formamide are used. The reaction mixture is stirred at 120 °C for 5 hours, then cooled and 200 ml of water are added. The precipitated crystalline product is filtered, washed twice with 50 ml of water each and recrystallized from ethanol. Thus 32.0 g of the desired compound are obtained, yield 80%. Mp.: 166--168 °C.

Example 3

N-(3,4-Dimethoxy-phenyl)-N-methyl-N-/¯3-(tetrahydro-2--furoyl-amino)-propyl7-N'-cyano-guanidine

One proceeds as described in Example 1 except that N-(tetrahydro-2-furoyl)-piperazine is replaced by 27.9 g (0.15 mole) of tetrahydro-N-/¯3-(methylamino)propyl7-2-furane-carboxamide. The reaction mixture is stirred at 60 °C for 8 hours. Thus 24.7 g of the desired compound are obtained, yield 63.5 %, mp.: 160-163 °C.

Example 4

2-/¯4-(Tetrahydro-2-furoyl)-piperazine7-4-amino-6,7-dimethoxy-quinazoline hydrochloride

A solution of 19.4 g (0.05 mole) of 4-(2-tetrahydro-2--furoyl)-piperazine-1-/¯N-cyano-N'-(3,4-dimethoxy-phenyl7-carboxamidine and 40 ml of diethylene glycol diethyl ether

is stirred at 180 °C for half an hour. The reaction mixture is cooled whereupon 100 ml of dichloromethane are added and the pH of the mixture is adjusted to 3-4 by adding an ispropanolic hydrogen chloride solution under intensive stirring and cooling with icecold water. During acidification the precipitation of crystals begins. The mixture is stirred at 0-5 °C for a further hour, the precipitated product is filtered and crystallized from isopropanol. Thus 15.6 g of the desired compound are obtained, yield 73.5 %, mp.: 277-279 °C.

Example 5

2-/¯4-(Tetrahydro-2-furoyl)-piperazinyl7-4-amino-6,7--dimethoxy-quinazoline hydrochloride

One proceeds as described in Example 4 except that as solvent 40 ml of dimethyl formamide are used and the reaction mixture is heated to boiling at 154 °C for one hour and a half. After cooling 200 ml of water are added, the precipitated product is filtered, washed twice with 100 ml of water each, suspended in 100 ml of methanol and the pH of the mixture is adjusted to 3-4 by adding isopropanol containing hydrogen chloride. The precipitated crystals are filtered and recrystallized from isopropanol. Thus 11.5 g of the desired compound are obtained, yield 54.2 %.

Example 6

2-/¯4-(Tetrahydro-2-furoyl)-piperazinyl7-4-amino-6,7-dimethoxy-quinazoline hydrochloride

One proceeds as described in Example 4 except that in place of diethylene glycol diethyl ether 30 ml of

sulfolane are used as solvent. The reaction mixture is stirred at 280 °C for a quarter of an hour.Thus 12.29 g of the desired compound are obtained, yield 57.5 %.

Example 7

N-/3-/(4-Amino-6,7-dimethoxy-2-quanizolinyl)-methyl-amino/-propyl/-tetrahydro-2-furane-carboxamide hydro-chloride

4.1 g (0.03 mole) of phosphorous trichloride are added to 40 ml of phosphorous oxychloride under cooling and stirring whereupon the mixture is stirred for 10 minutes and thereafter 11.7 g (0.03 mole) of N-(3,4-dimethoxy-phenyl)--N-methyl-N-/3-(tetrahydro-2-furoylamino)-propyl/-N-cyano--guanidine are added. The temperature is slowly raised to 70 °C and the reaction mixture is kept at this temperature for 2.5 hours. The excess of phosphorous oxychloride is evaporated in vacuo. To the residue slowly icecold water is added. The precipitated crude product is recrystallized from ethanol. Thus 9.6 g of the desired compound are obtained, yield 75%, mp.: 223-225 °C.

Example 8

N-/3-/(4-Amino-6,7-dimethoxy-2-quinazolinyl)-methyl-amino/-propyl/-tetrahydro-2-furane-carboxamide hydro-chloride

One proceeds as described in Example 7 except that in place of phosphorous trichloride 6.2 g (0.03 mole) of phosphorous pentachloride are used and the reaction mixture is stirred at 25 °C for 3 hours. Thus 8.5 g of the desired compound are obtained, yield 66.4 %.

Example 9

N-/~3-/~(4-Amino-6,7-dimethoxy-2-quinazolinyl)-methyl-amino7-propyl7-tetrahydro-2-furane-carboxamide hydrochloride

One proceeds as described in Example 7 except that in place of phosphorous trichloride 8.1 g (0.03 mole) of phosphorous tribromide are used and the reaction mixture is stirred at 180 °C for half an hour. Thus 7.8 g of the desired compound are obtained, yield 61%.

Example 10

N-/~3-/~(4-Amino-6,7-dimethoxy-2-quinazolinyl)-methyl-amino7-propyl7-tetrahydro-2-furane-carboxamide hydrochloride

One proceeds as described in Example 7 except that the mixture is saturated by introducing gaseous hydrogen chloride. The reaction mixture is stirred at first at 25-30 °C for 15 minutes and finally at 70-75 °C for an hour. Thus 8.5 g of the desired compound are obtained, yield 66.4 %.

Example 11

2-/~4-(Tetrahydro-2-furoyl)-piperazinyl7-4-amino-6,7--dimethoxy-quinazoline hydrochloride

A solution of 25.1 g (0.1 mole) of N-cyano-N'-(3,4-dimethoxy-phenyl)-S-methyl-isothiourea and 27.6 g (0.15 mole) of N-(tetrahydro-2-furoyl)-piperazine in 50 ml of dimethyl formamide is heated to boiling at 155-160 °C for 5 hours. The reaction mixture is cooled, 200 ml of water are added, the precipitated product is filtered, washed twice with 100 ml of water each, suspended in 100 ml of methanol and the pH

of the suspension is adjusted to 3-4 by adding isopropanol containing hydrogen chloride. The precipitated crystals are filtered off and recrystallized from isopropanol. Thus 19.5g of the desired compound are obtained, yield 46%, mp.: 277-279 °C.

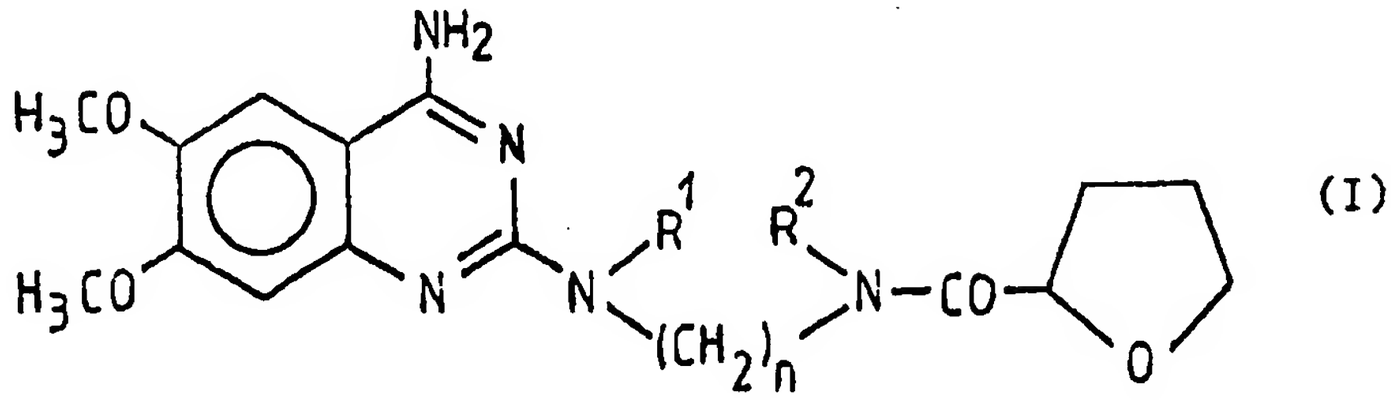
Example 12

2-/4-(Tetrahydro-2-furoyl)-piperazinyl/-4-amino-6,7-dimethoxy-quinazoline hydrochloride

One proceeds as described in Example 11 except that in place of dimethyl formamide 100 ml of diethylene glycol diethyl ether are used as solvent, and the reaction mixture is heated to boiling at 180 °C for 2 hours. After cooling 100 ml of dichloroethane are added and the pH of the mixture is adjusted to 3-4 by adding isopropanol containing hydrogen chloride under cooling with icecold water and vigorous stirring. The mixture is stirred at 0-5 °C for an hour, the precipitated product is filtered and recrystallized from isopropanol. Thus 20.8 g of the desired compound are obtained, yield 49%, mp.: 277-279 °C.

CLAIMS

1. A process for the preparation of quinazcline derivatives of the general Formula I



(I)

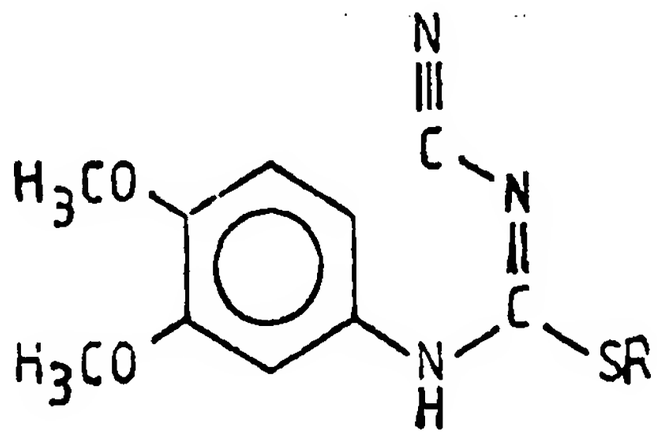
/ wherein

R^1 and R^2 may be the same or different and stand for hydrogen or lower alkyl or together form an ethylene ($-CH_2-CH_2-$) or trimethylene ($-CH_2-CH_2-CH_2-$) group; and

n is the integer number 2 or 3

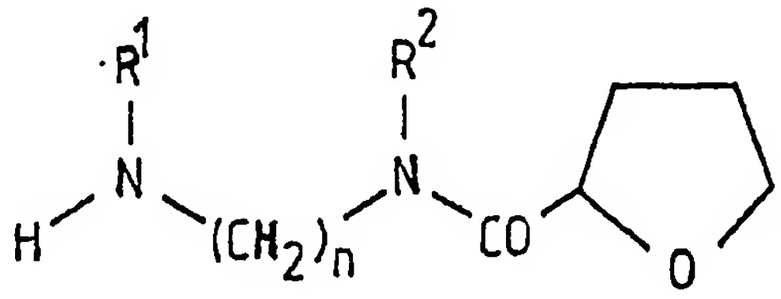
and pharmaceutically acceptable acid addition salts thereof, which comprises

a) reacting an isothiourea derivative of the general Formula III



(III)

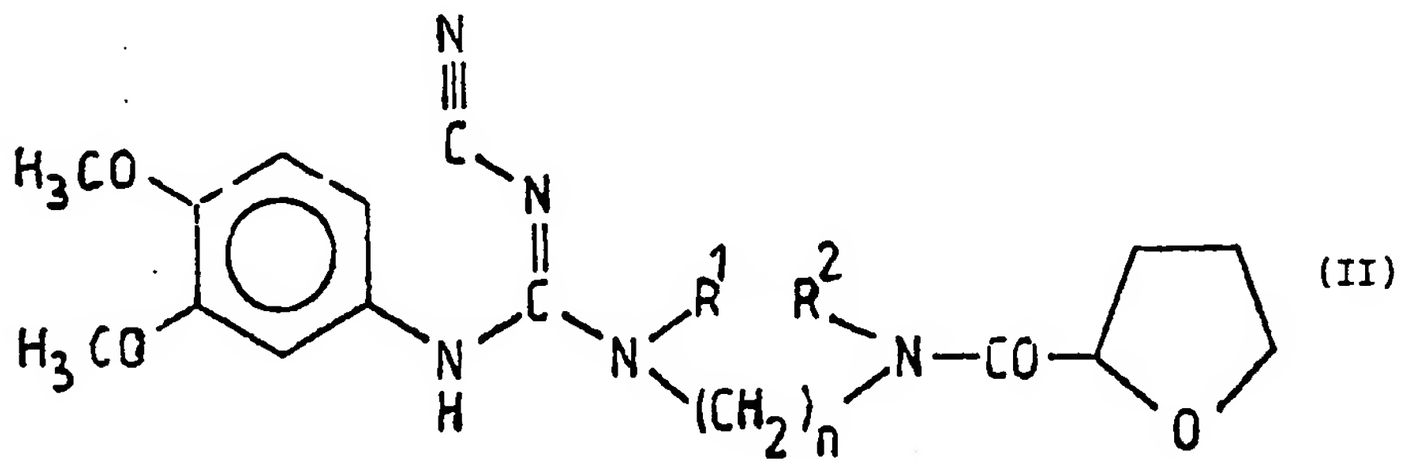
/ wherein R stands for lower alkyl or phenyl-lower alkyl, where the phenyl ring of the latter group may be optionally substituted by one or more lower alkyl group(s) and/or halogen atom(s)/ with an amine of the general Formula IV



(IV)

(wherein R^1, R^2 and n are as stated above) at a temperature between 150 °C and 280 °C; or

b) cyclising a compound of the general Formula II



(II)

(wherein R^1, R^2 and n are as stated above) optionally in the presence of a catalyst;

and, if desired, converting a compound of the general

Formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

2. Process according to Claim 1a), which comprises carrying out the reaction in a solvent which has a boiling point above 150 °C, preferably in dimethyl formamide, dimethyl acetamide or sulfolane.

3. Process according to Claim 1a), which comprises carrying out the process at a temperature between 150 °C and 220 °C.

4. Process according to Claim 1b), which comprises carrying out the reaction at a temperature between 150 °C and 280 °C, preferably at 150-220 °C.

5. Process according to Claim 1b) or 4, which comprises carrying out the reaction in the absence of a solvent.

6. Process according to Claim 1b) or 4, which comprises carrying out the reaction in the presence of a solvent.

7. Process according to Claim 1b, which comprises carrying out the reaction in the presence of a catalyst.

8. Process according to Claim 7, which comprises carrying out the reaction at a temperature between 25 °C and 130 °C, preferably at 70-100 °C.

9. Process according to any of Claims 7 and 8, which comprises using phosphorous oxychloride as solvent and phosphorous trichloride, phosphorous tribromide or a Lewis acid as catalyst.

10. Process according to any of Claims 1-9 for the preparation of a compound of the general Formula I, wherein R^1 stands for methyl; R^2 is hydrogen and n = 3, which comprises using as starting materials compounds of the general Formula II, III and IV, in which R^1, R^2 and n are as stated in the preamble of this Claim.

11. Process according to any of Claims 1-9 for the preparation of a compound of the general Formula I, wherein R^1 and R^2 together form an ethylene group ($-CH_2-CH_2-$) and n = 2, which comprises using as starting material compounds of the general Formulae II, III and IV, in which R^1, R^2 and n have the same meaning as stated in the preamble of this Claim.

12. A process as claimed in claim 1 as substantially described herein with particular reference to the Examples.

13. Compounds of the general Formula I, whenever prepared by a process according to any of Claims 1-12.

14. Compounds of the general Formula II as depicted in claim 1 /wherein

R^1 and R^2 independently may be the same or different and stand for hydrogen or lower alkyl or together form an ethylene - ($-CH_2-CH_2-$) or trimethylene ($-CH_2-CH_2-CH_2-$) group; and

n is the integer number 2 or 3/.

15. Process for the preparation of compounds of the general Formula II (wherein R^1, R^2 and n are as stated in Claim 14), which comprises reacting an isothiourea derivative of the general Formula III /wherein R stands

for lower alkyl or phenyl-lower alkyl, where the phenyl ring of the latter group may be optionally substituted by one or more lower alkyl group(s) and/or halogen atom(s)7 with an amine of the general Formula IV (wherein R^1, R^2 and n are as stated above) at a temperature not exceeding 130 °C.

16. Process according to Claim 15, which comprises carrying out the reaction in an alcohol or a polar aprotic solvent.

17. Process according to Claim 16, which comprises carrying out the reaction in isopropanol.

18. Process according to Claim 16, which comprises carrying out the reaction in dimethyl formamide.

19. Process according to any of Claims 15-18, which comprises carrying out the reaction at a temperature between 25 °C and 130 °C.

20. A process as claimed in claim 15, substantially as hereinbefore described in any of Examples 1 to 3.

21. The title compounds of any one of Examples 1 to 3.

22. Compounds of the general Formula II when prepared by a process as claimed in any one of claims 15 to 20.

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